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Validation and Comparison of the Long-Term Prognostic Capability of the SYNTAX Score-II Among 1,528 Consecutive Patients Who Underwent Left Main Percutaneous Coronary Intervention

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ABSTRACT

OBJECTIVES This study sought to evaluate the long-term prognostic capacity of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score II (SS-II) and compare it with other risk scores among patients undergoing left main percutaneous coronary intervention (LM-PCI).

BACKGROUND Recently, the SS-II was developed in an attempt to individualize and help the decision-making process between PCI and coronary artery bypass graft (CABG) surgery in the management of complex coronary artery disease (CAD). However, there is a paucity of data regarding the utility of SS-II in patients undergoing LM-PCI.

METHODS Data from 1,528 consecutive patients from a single center undergoing unprotected LM-PCI were prospectively collected. The SS-II and other scores were then derived using patients' baseline clinical characteristics. Patients were stratified according to tertiles of SS-II for PCI: SS-II ≤21 (n = 508), SS-II >21 and ≤28 (n = 480), and >28 (n = 540). Predictive capability for long-term mortality was compared between angiographic scores and scores combining both angiographic and clinical variables.

RESULTS At a mean follow-up of 4.4 years, mortality in the first, second, and third SS-II tertiles was 1.8%, 3.5%, and 9.4%, respectively ($p < 0.0001$). Multivariate analysis showed SS-II to be a strong independent predictor of mortality (hazard ratio: 1.76, 95% confidence interval: 1.10 to 2.82; $p = 0.02$) after LM-PCI. When compared with the angiographic SS, scores combining both clinical and angiographic variables, such as the SS-II, were superior in terms of long-term prognostication.

CONCLUSIONS Results of this large series of consecutive patients who underwent unprotected LM-PCI suggested that the SS-II has better long-term prognostic power in terms of mortality compared with the original purely angiographic SS. (J Am Coll Cardiol Intv 2014;7:1128–37) © 2014 by the American College of Cardiology Foundation.

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The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) has been shown to be predictive of adverse outcomes among patients undergoing percutaneous coronary intervention (PCI) (1–8). Despite its broad recognition as an important tool in the decision-making process to select the most appropriate revascularization strategy between PCI and coronary artery bypass graft (CABG) surgery (9–11), the SS has not shown predictive capacity among patients undergoing CABG (12–16). Moreover, the lack of inclusion of clinical variables in the SS has been identified as a major limitation in its capacity to accurately stratify patients with complex coronary artery disease (CAD). Several groups have demonstrated that the addition of clinical variables increased the stratification capability of the SS (17–21). With these limitations in mind, the SYNTAX score II (SS-II) was recently developed, incorporating a combination of angiographic and clinical variables that have been shown to modify the anatomic SS threshold where the equipoise for long-term mortality is reached between PCI and CABG (22). The SS-II, by incorporating both of these important angiographic (anatomic SS) and clinical variables (age, sex, left ventricular ejection fraction, creatinine clearance, chronic obstructive pulmonary disease, and peripheral vascular disease), ensures a more accurate and individualized mortality prediction, resulting in a more clinically useful tool for bedside decision making in the management of complex CAD. Although the SS-II was internally validated in the SYNTAX trial (3) and externally validated in the DELTA registry (23), no other large registries have confirmed its utility, especially among patients undergoing left main (LM) PCI only. Moreover, retrospective validation using a registry, where patients have been treated according to whether they were more clinically suitable for PCI or CABG, is associated with an important bias. Therefore, we sought to evaluate and confirm the prognostic capacity of the SS-II among patients undergoing LM-PCI only and to compare its predictive capability with other existing scoring systems.

METHODS

STUDY POPULATION. Data from all consecutive patients from a single center (Fu Wai Hospital, National Center for Cardiovascular Diseases, Beijing, China) undergoing LM-PCI were prospectively collected. After excluding patients with previous CABG, the SS (1) and the residual SS (rSS) (24–28) from all coronary angiograms, using standard quantitative coronary analysis methodology, were assessed by an independent angiographic core laboratory blinded to clinical outcomes. The SS-II (for both PCI and CABG) were derived by using patients' baseline clinical characteristics as previously described (22). Briefly, the baseline SS was computed, and, according to the pre-defined algorithm, points were added taking into account 6 other clinical variables (age, sex, left ventricular ejection fraction, creatinine clearance [in millimeters per min], chronic obstructive pulmonary disease, and peripheral vascular disease), leading to the SS-II. Patients were stratified and compared according to tertiles of SS-II for PCI (22).

Additionally, SS-II for PCI and SS-II for CABG were compared for each patient. If SS-II for PCI was greater than the SS-II for CABG (suggesting that CABG would have been a more favorable strategy of revascularization), the patients were labeled as SS-II favoring CABG. Conversely, if the SS-II for PCI was less than the SS-II for CABG, the patient was deemed to be a better candidate for PCI and was labeled as SS-II favoring PCI. Outcomes of both groups (SS-II favoring PCI vs. SS-II favoring CABG) were compared.

STUDY ENDPOINTS. Our primary objective was to assess the capacity of the SS-II for PCI to appropriately stratify the risk of all-cause mortality in patients undergoing LM-PCI. The association between the SS-II for PCI and the occurrence of adverse ischemic outcomes, including death, cardiac death, myocardial infarction (MI), unplanned target vessel revascularization (TVR) for ischemia, Academic Research Consortium-defined stent thrombosis (29), and major adverse cardiac and cerebrovascular events were assessed as well. The latter was defined as the composite of all-cause death, stroke, MI, or unplanned TVR for ischemia. All endpoints were adjudicated centrally by 2 independent cardiologists, and disagreement was resolved by consensus.

We also compared the prognostic value of the SS-II for PCI with the purely angiographic SS (1) and other scores (18,19,24), using the receiver-operating characteristic curves, net reclassification improvement (NRI), and the integrated discriminatory index (IDI) (30).

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD and were compared using the Student *t* test or the Mann-Whitney rank sum test, as appropriate. Categorical variables were compared with the chi-square or Fisher exact test. Clinical outcomes were determined using Kaplan-Meier methodology

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
HR = hazard ratio
IDI = integrated discrimination improvement
LM = left main
MI = myocardial infarction
NRI = net reclassification index
PCI = percutaneous coronary intervention
rSS = residual SYNTAX score
SS = SYNTAX score
SS-II = SYNTAX score II

and compared using the log-rank test. To test for possible associations between the SS-II and the rates of long-term mortality, stepwise Cox multivariable regression analysis was used, with variable entry/stay criteria of 0.1/0.1. In addition to SS-II risk score, variables historically known to be associated with long-term mortality were included in the model. The proportional hazard assumption was verified for each endpoint using the Supremum test. Receiver-operating characteristic curves were used to compare the prognostic ability of the various risk scores to predict the rates of ischemic adverse events. Risk scores considered were the purely angiographic SS, rSS, the clinical SS, the logistic SS, and SS-II risk scores. We also calculated the ability of the SS-II to reclassify the risk of ischemic adverse events at long-term follow-up beyond the anatomic SS using the NRI as well as the IDI (30). A p value <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS AND BASELINE CHARACTERISTICS. From January 2004 to December 2010, 1,528 patients underwent unprotected LM-PCI at Fu Wai Hospital, National Center for Cardiovascular Diseases, Beijing, China. Among the entire cohort, mean values for baseline SS and rSS were 23.9 ± 7.1 and 4.4 ± 5.9, respectively, and the calculated SS-II for PCI was 25.6 ± 7.8, and the SS-II for CABG was 26.7 ± 9.6. Of the 1,528 patients, 963 (63%) had SS-II for PCI less than the SS-II for CABG, and 565 (37%) had a SS-II for

TABLE 1 Baseline Clinical Characteristics According to SS-II for PCI Tertiles

	Low Tertile SS-II ≤21 (n = 508)	Intermediate Tertile SS-II >21 and ≤28 (n = 480)	High Tertile SS-II >28 (n = 540)	p Value
Age, yrs	50.3 ± 7.3	60.3 ± 7.8	68.8 ± 7.3	<0.0001
Female	22/508 (4.3)	108/480 (22.5)	194/540 (35.9)	<0.0001
Weight, kg	76.6 ± 9.8	72.4 ± 10.0	67.9 ± 9.9	<0.0001
Height, cm	170.5 ± 5.8	167.5 ± 6.8	164.8 ± 8.0	<0.0001
Smoking history				<0.0001
Current smoker	224/508 (44.1)	116/480 (24.2)	93/540 (17.2)	
Ex-smoker	96/508 (18.9)	86/480 (17.9)	91/540 (16.9)	
None	188/508 (37.0)	278/480 (57.9)	356/540 (65.9)	
Diabetes mellitus	115/508 (22.6)	118/480 (24.6)	136/540 (25.2)	0.60
Hypertension	237/508 (46.7)	272/480 (56.7)	315/540 (58.3)	0.0003
Hyperlipidemia	276/508 (54.3)	236/480 (49.2)	254/540 (47.0)	0.05
Family history of CAD	77/508 (15.2)	51/480 (10.6)	55/540 (10.2)	0.03
Previous myocardial infarction	110/508 (21.7)	115/480 (24.0)	162/540 (30.0)	0.006
Previous PCI	115/508 (22.6)	106/480 (22.1)	122/540 (22.6)	0.97
Previous stroke	18/508 (3.5)	33/480 (6.9)	49/540 (9.1)	0.0009
Peripheral vascular disease	0/508 (0.0)	5/480 (1.0)	75/540 (13.9)	<0.0001
COPD	2/508 (0.4)	3/480 (0.6)	7/540 (1.3)	0.23
LVEF, %	63.6 ± 6.3	63.2 ± 7.0	61.7 ± 8.9	<0.0001
Creatinine, μmol/l	78.0 ± 13.6	77.1 ± 16.5	89.5 ± 22.3	<0.0001
Creatinine clearance, ml/min	110.3 ± 24.3	94.1 ± 26.0	68.4 ± 19.1	<0.0001
Clinical presentation				0.29
Stable angina	166/508 (32.7)	133/480 (27.7)	165/540 (30.6)	
Acute coronary syndrome	328/508 (64.6)	335/480 (69.8)	35/540 (65.6)	
Silent ischemia	14/508 (2.8)	12/480 (2.5)	21/540 (3.9)	
PCI access				0.005
Radial approach	316/508 (62.2)	256/480 (53.3)	289/540 (53.5)	
Femoral approach	192/508 (37.8)	224/480 (46.7)	251/540 (46.5)	
PCI procedure duration, min	51.4 ± 33.4	56.7 ± 39.4	55.8 ± 35.0	0.05
Follow-up duration, days	1,601.2 ± 675.0	1,589.5 ± 786.8	1,584.7 ± 745.7	0.93
DAPT >1 yr	488/508 (96.1)	455/480 (94.8)	513/540 (95.0)	0.59

Values are n/N (%) or mean ± SD.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DAPT = dual-antiplatelet therapy; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; SS-II = SYNTAX score II.

CABG less than the SS-II for PCI. Baseline characteristics stratified by tertiles of SS-II for PCI are presented in Table 1. Patients in the upper tertile were older, more frequently female, and shorter; more frequently had a previous MI or stroke; and were more often nonsmokers with lower weight, ejection fraction, and pre-PCI creatinine clearance. Coronary disease at baseline was significantly more extensive

TABLE 2 Angiographic and Procedural Characteristics According to SS-II for PCI Tertiles

	Low Tertile SS-II ≤21 (n = 508)	Intermediate Tertile SS-II >21 and ≤28 (n = 480)	High Tertile SS-II >28 (n = 540)	p Value
Angiographic findings				<0.0001
Isolated LM	67/508 (13.2)	22/480 (4.6)	21/540 (3.9)	
LM + 1 vessel	154/508 (30.3)	97/480 (20.2)	63/540 (11.7)	
LM + 2 vessels	173/508 (34.1)	172/480 (35.8)	215/540 (39.8)	
LM + 3 vessels	114/508 (22.4)	189/480 (39.4)	241/540 (44.6)	
LM lesion type				0.44
De novo	496/508 (97.6)	462/480 (96.3)	524/540 (97.0)	
Restenosis	12/508 (2.4)	18/480 (3.8)	16/540 (3.0)	
LM lesion length, mm	20.4 ± 14.5	21.9 ± 15.4	23.4 ± 15.8	0.006
LM lesion location				0.004
Ostium	66/508 (13.0)	51/480 (10.6)	58/540 (10.7)	
Shaft	50/508 (9.8)	24/480 (5.0)	26/540 (4.8)	
Distal bifurcation	392/508 (77.2)	405/480 (84.4)	456/540 (84.4)	
LM bifurcation Medina classification				0.01
0,0,1	1/392 (0.3)	1/405 (0.2)	4/456 (0.9)	
0,1,0	11/392 (2.8)	9/405 (2.2)	15/456 (3.3)	
0,1,1	6/392 (1.5)	6/405 (1.5)	8/456 (1.8)	
1,0,0	25/392 (6.4)	12/405 (3.0)	16/456 (3.5)	
1,0,1	34/392 (8.7)	32/405 (7.9)	31/456 (6.8)	
1,1,0	203/392 (51.8)	180/405 (44.4)	194/456 (42.5)	
1,1,1	112/392 (28.6)	165/405 (40.7)	188/456 (41.2)	
LM bifurcation with final kissing	198/392 (50.5)	203/405 (50.1)	208/456 (45.6)	0.28
LM bifurcation with 2-stent technique	128/392 (32.7)	137/405 (33.8)	148/456 (32.5)	0.87
Type of 2-stent technique				0.29
Culotte	9/128 (7.0)	6/137 (4.4)	7/148 (4.7)	
Crush	89/128 (69.5)	96/1377 (0.1)	95/148 (64.2)	
T-stent	15/128 (11.7)	14/137 (10.2)	29/148 (19.6)	
Kissing stent	15/128 (11.7)	21/137 (15.3)	17/148 (11.5)	
No. of target lesions	1.62 ± 0.77	1.75 ± 0.84	1.71 ± 0.78	0.03
Stent implantation	504/508 (99.2)	474/480 (98.8)	534/540 (98.9)	0.76
Type of stents in LM				
BMS+PTCA	3.0 (15/508)	4.2 (20/480)	5.4 (29/540)	0.09
First DES	65.4 (332/508)	63.5 (305/480)	58.3 (315/540)	
Second DES	31.7 (161/508)	32.3 (155/480)	36.3 (196/540)	
Stent length	25.4 ± 14.9	27.5 ± 15.8	29.2 ± 17.3	0.0009
Stent diameter	3.5 ± 0.5	3.4 ± 0.5	3.3 ± 0.5	<0.0001
No. of stents per patient	1.96 ± 1.06	2.21 ± 1.14	2.31 ± 1.22	<0.0001
IVUS use	213/508 (41.9)	176/480 (36.7)	186/540 (34.4)	0.04
Complications during procedure	13/508 (2.6)	23/480 (4.8)	25/540 (4.6)	0.11
Procedural success	505/508 (99.4)	471/480 (98.1)	531/540 (98.3)	0.13
Baseline SS	20.72 ± 5.94	24.69 ± 6.81	26.31 ± 7.14	<0.0001
Residual SS	2.67 ± 3.78	4.64 ± 6.07	5.86 ± 6.82	<0.0001
Modified ACEF score	0.80 ± 0.15	0.99 ± 0.24	1.80 ± 0.98	<0.0001
Clinical SS	16.43 ± 4.95	24.33 ± 7.99	47.06 ± 28.61	<0.0001
Logistic Clinical SYNTAX score	5.49 ± 1.32	8.30 ± 1.83	11.06 ± 2.40	<0.0001
SS-II: PCI	17.58 ± 2.17	24.32 ± 2.04	34.27 ± 5.29	<0.0001
SS-II: CABG	18.85 ± 5.46	25.80 ± 7.50	34.92 ± 7.61	<0.0001

Values are n/N (%) or mean ± SD.

ACEF = age, creatinine, ejection fraction; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; DES = drug-eluting stent(s); IVUS = intravascular ultrasound; LM = left main; PTCA = percutaneous transluminal coronary angioplasty; SS = SYNTAX score; other abbreviations as in Table 1.

TABLE 3 Adverse Ischemic Outcomes at 4.4 Years of Follow-up According to SS-II Tertiles

	Low Tertile SS-II ≤21 (n = 508)	Intermediate Tertile SS-II >21 and ≤28 (n = 480)	High Tertile SS-II >28 (n = 540)	p Value (Trend)	p Value* 1 vs. 2	p Value* 2 vs. 3	p Value* 1 vs. 3
All-cause mortality	9 (1.8)	17 (3.5)	51 (9.4)	<0.0001	0.08	0.0001	<0.0001
Cardiac mortality	7 (1.4)	11 (2.3)	29 (5.4)	0.0005	0.28	0.01	0.0002
Noncardiac mortality	2 (0.4)	6 (1.3)	22 (4.1)	<0.0001	0.17	0.004	<0.0001
Stroke	9 (1.8)	9 (1.9)	15 (2.8)	0.48	0.90	0.34	0.27
MI	19 (3.7)	35 (7.3)	61 (11.3)	<0.0001	0.01	0.03	<0.0001
Q-wave	7 (1.4)	12 (2.5)	30 (5.6)	0.0004	0.20	0.01	0.0001
Clinically driven TVR	49 (9.6)	44 (9.2)	51 (9.4)	0.97	0.80	0.88	0.91
All-cause mortality/stroke/MI	32 (6.3)	52 (10.8)	102 (18.9)	<0.0001	0.01	0.0003	<0.0001
MACCE	94 (18.5)	109 (22.7)	158 (29.3)	0.0002	0.10	0.01	<0.0001
ARC stent thrombosis (definite/probable)	6 (1.2)	6 (1.3)	14 (2.6)	0.15	0.92	0.12	0.09

Values are n (%). Kaplan-Meier rates estimated at a mean follow-up of 4.4 years. *Bonferroni correction was performed. A p value <0.0167 was considered statistically significant.

ARC = Academic Research Consortium; MACCE = major adverse cardiac cerebrovascular events (the composite of all-cause death, stroke, MI, or clinically driven TVR); MI = myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Table 1.

and more complex in the upper SS-II tertiles, with higher rates of 2- or 3-vessel disease, higher baseline SS, and higher rSS (Table 2).

ADVERSE ISCHEMIC OUTCOMES. At 4.4-year follow-up, the rates of all-cause death, cardiac death, MI, and ischemic-driven TVR in the overall cohort were 5%, 3.1%, 7.5%, and 9.4%, respectively. Clinical outcomes stratified according to SS-II tertiles are shown in Table 3 and Figures 1A to 1F. At a mean follow-up of 4.4 years, rates of death, cardiac death, MI, and composite ischemic endpoint were significantly higher in the upper tertile than in the intermediate or lower tertiles. After multivariate analysis, SS-II was an independent predictor of long-term mortality (hazard ratio [HR]: 1.76, 95% confidence interval [CI]: 1.10 to 2.82; p = 0.02) after LM-PCI (Table 4). After adjusting for SS-II, other independent predictors of long-term mortality among the entire cohort include baseline left ventricular ejection fraction (HR: 0.96, 95% CI: 0.93 to 0.99; p = 0.003), the presence chronic obstructive pulmonary disease (HR: 3.28, 95% CI: 1.00 to 10.75; p = 0.05), and history of (HR: 1.69, 95% CI: 1.03 to 2.78; p = 0.03).

The rates of adverse events stratified by whether the SS-II for PCI was greater than the SS-II for CABG for a given patient (suggesting that CABG would have been a more favorable strategy for revascularization) are presented in Table 5. Mortality was numerically higher in the group with an SS-II for PCI greater than the SS-II for CABG compared with the group in which the SS-II for PCI was less than the SS-for CABG (5.8% vs. 4.6%, respectively, p = 0.28).

PREDICTIVE CAPABILITY OF SS-II AND OTHER SCORING SYSTEMS. Compared with the strictly anatomic SS, scoring systems combining clinical variables and anatomic SS (clinical SS, logistic SS, and SS-II) had better discrimination and similar calibration for the prediction of long-term mortality (Figure 2, Table 6). Specifically, the SS-II had better discrimination (C-statistic: baseline SS = 0.591 vs. SS-II = 0.694, p < 0.0001) than the anatomic SS alone, with both models showing relatively good calibration and no lack of fitting (chi-square baseline SS = 3.45, p = 0.90 vs. chi-square SS-II = 6.58, p = 0.58).

The SS-II significantly improved mortality predictability by appropriately reclassifying several patients (Table 7). In 77 patients who died at follow-up, SS-II improved classification in 28 and worsened it in 11, with a net gain in reclassification of 17 (22%) compared with the anatomic SS. In the 1,451 patients who did not die, SS-II improved classification in 438 and worsened it in 390, for net gain in reclassification of 48 (3%). The NRI of the SS-II over the anatomic SS was 25% (95% CI: 9.8 to 41; p = 0.002). The magnitude of change was relatively important, with an IDI of 1.5% (95% CI: 0.51 to 2.4; p = 0.003). Improvement in patients' reclassification compared with the angiographic SS in terms of long-term mortality was seen across all scoring systems that combined clinical and angiographic variables (Online Tables 1 and 2).

DISCUSSION

The present report is the first and the largest real-world study to specifically evaluate and compare

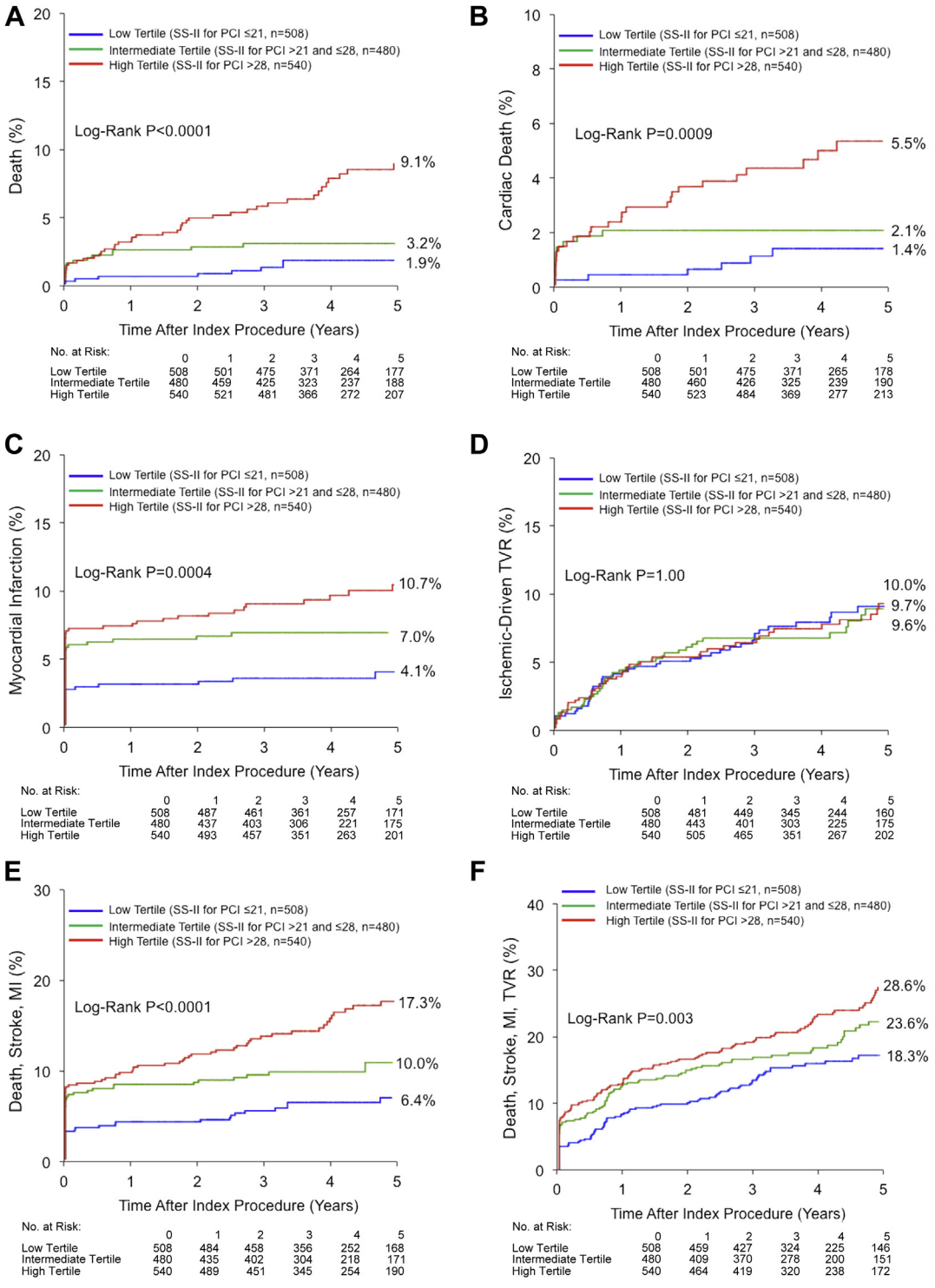

FIGURE 1 Kaplan-Meier Curves Showing Event Rates Stratified by the SS-II Through 5 Years

All-cause death **(A)**; cardiac death **(B)**; myocardial infarction **(C)**; ischemic-driven target vessel revascularization **(D)**; composite of death, myocardial infarction, and stroke **(E)**; and the composite of death, myocardial infarction, ischemic target vessel revascularization, and stroke **(F)** stratified by tertiles of SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score II (SS-II). Except for rate of target vessel revascularization, event rates significantly increased within each SS-II tertile.

TABLE 4 Predictors of Long-Term Mortality After LM PCI

Variable	Adjusted Hazard Ratio (95% CI)	p Value
Multivariable Cox Regression Analysis		
Age (per 10-yr increase)	1.61 (1.18–2.18)	0.002
Male	1.30 (0.70–2.35)	0.42
LVEF (per 10% increase)	0.57 (0.43–0.74)	<0.0001
COPD	4.20 (1.31–13.46)	0.02
Creatinine clearance (per 10-ml increase)	0.99 (0.88–1.11)	0.85
Previous MI	1.65 (1.01–2.71)	0.05
History of stroke	1.60 (0.81–3.13)	0.18
Multivariable Cox Regression Analysis With SS-II		
Age (per 10-yr increase)	1.30 (0.92–1.83)	0.14
Male	1.79 (0.92–3.49)	0.08
LVEF (per 10% increase)	0.65 (0.49–0.86)	0.003
COPD	3.28 (1.00–10.75)	0.05
Creatinine clearance (per 10-ml increase)	1.06 (0.95–1.17)	0.32
Previous MI	1.69 (1.03–2.78)	0.04
History of stroke	1.60 (0.82–3.15)	0.17
SS-II for PCI (per 10-point increase)	1.76 (1.10–2.82)	0.02

Each model is adjusted for the variables shown in the table.
CI = confidence interval; other abbreviations as in Tables 1 and 3.

the long-term prognostic capacity of the SS-II and other risk scores to the strictly anatomic SS among a cohort of consecutive patients undergoing LM-PCI. The main results of the present study are as follows: 1) within a population of patients undergoing LM-PCI, the SS-II for PCI was able to risk-stratify patients and predict long-term adverse ischemic events, including mortality; and 2) scoring systems combining anatomic SS and clinical variables, such as the SS-II, demonstrated better predictability for long-term mortality compared with the strictly anatomic SS among a population with complex CAD undergoing LM-PCI.

TABLE 5 Adverse Ischemic Outcomes at 4.4 Years of Follow-Up According to SS-II Favoring PCI Versus CABG

	SS-II Favoring PCI (n = 963)	SS-II Favoring CABG (n = 565)	p Value
All-cause mortality	44 (4.6)	33 (5.8)	0.28
Cardiac mortality	22 (2.3)	25 (4.4)	0.02
Noncardiac mortality	22 (2.3)	8 (1.4)	0.23
Stroke	25 (2.6)	8 (1.4)	0.11
MI	70 (7.3)	45 (8.0)	0.62
Q-wave	25 (2.6)	24 (4.2)	0.08
Clinically driven revascularization	139 (14.4)	71 (12.6)	0.30
All-cause mortality/stroke/MI	119 (12.4)	67 (11.9)	0.77
MACCE	239 (24.8)	122 (21.6)	0.15
ARC stent thrombosis (definite/probable)	15 (1.6)	11 (1.9)	0.57

Values are n (%). Kaplan-Meier rates estimated at a mean follow-up of 4.4 years.
Abbreviations as in Tables 1, 2, and 3.

Superiority of scoring systems combining both anatomic and clinical variables compared with the strictly anatomic SS has been demonstrated by several groups (31). Girasis et al. (32) were among the first to show that the addition of patient age, creatinine, and ejection fraction (a combination known as ACEF) to the SS to form the clinical SS significantly improved the ability to predict events for patients undergoing PCI in the SIRTAX trial (SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization) (33). Actually, similar to our findings, the clinical SS significantly improved all-cause mortality prediction at 5 years compared with the SS, with a better discrimination power for all-cause mortality (area under the curve [AUC]: 0.66, 95% CI: 0.59 to 0.73 vs. AUC: 0.58, 95% CI: 0.51 to 0.65; $p < 0.001$), and cardiac mortality (AUC: 0.72, 95% CI: 0.63 to 0.81 vs. AUC: 0.63, 95% CI: 0.54 to 0.72; $p < 0.002$), but not for the composite ischemic endpoint (death due to cardiac causes, MI, and ischemia-driven target lesion revascularization). Similar results were demonstrated in the ARTS II (Arterial Revascularization Therapies Study II), with the clinical SS significantly improving the predictability of both mortality and composite ischemic endpoints at 5 years (18). Farooq et al. (19) also demonstrated that combining meaningful clinical variables, previously selected on the basis of their logistic regression coefficients, with anatomic SS—the so-called logistic SS—results in an enhanced and more individualized patient stratification. Finally, several groups also demonstrated the incremental prognostic value of the Global Risk Classification score, which combines the EuroSCORE (European System for Cardiac Operative Risk Evaluation) and SS to improve risk prediction of adverse cardiovascular events compared with the SS alone in patients with complex CAD undergoing LM revascularization (17,20).

Development of the SS-II was initially intended to improve and individualize patient stratification as a way to help clinicians decide on the most appropriate revascularization strategy (PCI vs. CABG). One of the main findings of the current report is that, among a cohort of "real-world" patients deemed suitable for LM-PCI, the SS-II was able to risk-stratify and identify patients who will eventually experience adverse events. The mean SS-II for PCI of the entire cohort was 25.6 ± 7.8, and the calculated SS-II for CABG among the entire cohort was 26.7 ± 9.6, suggesting that globally, according to SS-II stratification, this

cohort was more suitable for PCI than CABG. However, among those patients, ~40% had an SS-II for PCI higher than for CABG and were deemed to be better candidates for CABG per the SS-II algorithm. Mortality (especially cardiac mortality) was indeed slightly higher among such patients who underwent LM-PCI despite CABG being identified as the most favorable revascularization strategy. This finding importantly illustrates the predictive capability of the SS-II among a cohort of patients undergoing PCI only.

The SS-II was also shown here to improve predictability accuracy compared with the strictly anatomic baseline SS for long-term mortality. Indeed, SS-II reclassified patients 25% of the time compared with baseline SS. In fact, all the scoring systems combining the angiographic SS with clinical variables (i.e., clinical SS, logistic SS) substantially enhanced the prognostic ability of the anatomic SS.

Notably, the rSS (24,25) progressively increases within each tertile of the SS-II. This finding illustrates the already known correlation between baseline SS and rSS (24), and it confirms the capacity of the SS-II to identify patients who not only will more frequently have adverse events (death and MI) but also suboptimal revascularization.

In the SYNTAX trial, the lack of antiplatelet therapy at discharge, low ejection fraction, the presence of peripheral vascular disease, more advanced age, female sex, previous gastrointestinal bleeding, prescription of amiodarone at discharge, and a higher SS (per 10 points) were all independently associated with long-term mortality after PCI (34). Those variables were then integrated in the SS-II (22). However, the low number of patients undergoing LM-PCI (n = 347) and the low number of related deaths at 4 years (n = 37, 11.4%) limited the identification of predictors of long-term mortality after LM-PCI. On the other hand, our study, with ~5 times more patients undergoing LM-PCI (n = 1,528), and hence a higher number of deaths (n = 77, 5% long-term mortality), offers more power to identify meaningful predictors. Consideration and selection of those factors in a combined clinical/anatomic score could be of interest and refine even more the predictability of the SS-II, specifically for LM-PCI. Interestingly, similar to the SYNTAX trial, diabetes status was not identified as a predictor of long-term mortality.

STUDY LIMITATIONS. Despite being the first and largest report to validate the SS-II exclusively in a population of patients undergoing LM-PCI, this report has some limitations that should be acknowledged. First, it represents a single-center experience, with 6 highly experienced operators. This limitation is important because it may affect the generalizability of our findings. Indeed, neither the SS nor the SS-II accounts for operator experience, volume, or technical skill, and operators' expertise may have favorably influenced the prognosis of patients included in our study, especially in upper tertiles. Second, determination of the SS is associated with inter- and intraobserver variability (35), and physiological assessment (fractional flow reserve-guided) may help in reducing this variability (36). Another limitation is that the events were self-reported and not adjudicated, which might underestimate or overestimate the event rates. Third, discrimination issues have been raised regarding SS-II risk predictability and may have also affected our results (37). Fourth, our validation is restricted to patients undergoing

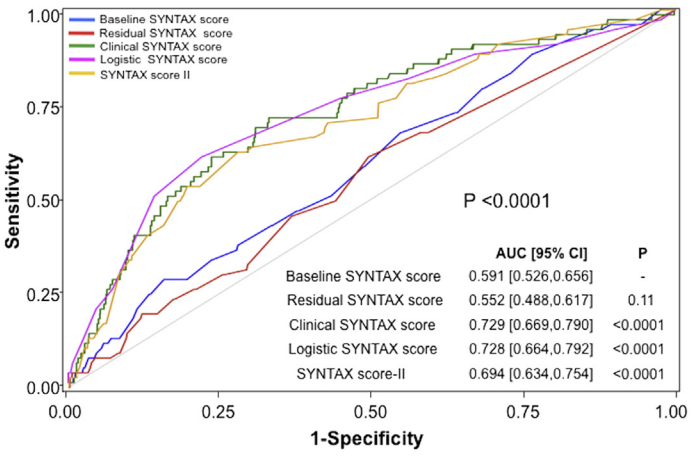

FIGURE 2 Receiver-Operating Characteristic Curve Analyses Comparing the SS With the Residual SS, the Clinical SS, the Logistic SS, and the SS-II for the Predictability of Long-Term Mortality

The addition of clinical variables to the anatomic SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) resulted in better discrimination compared with a strictly anatomic SS. The incremental value on mortality predictability was similar for all different clinical-anatomic scores compared with a strictly anatomic SS.

TABLE 6 Discrimination and Calibration of SYNTAX and Derived Scores for All-Cause Mortality at 4.4-Year Follow-Up

	AUC (95% CI)	p Value*	Hosmer-Lemeshow (p Value)
Anatomic SS	0.591 (0.526-0.656)	–	3.45 (0.90)
Residual SS	0.552 (0.488-0.617)	0.11	5.02 (0.76)
Clinical SS	0.729 (0.669-0.790)	<0.0001	10.76 (0.22)
Logistic clinical SS	0.728 (0.664-0.792)	<0.0001	9.47 (0.30)
SS-II for PCI	0.694 (0.634-0.754)	<0.0001	6.58 (0.58)

*For comparison between anatomic SYNTAX score and other scores.
AUC = area under the curve; other abbreviations as in Table 1.

TABLE 7 Reclassification of All-Cause Mortality by Combined Anatomic-Clinical Scores Versus Anatomic SS

	NRI or IDI	p Value
SS-II vs. anatomic SS		
NRI	0.25	0.002
IDI	0.015	0.003
Clinical SS vs. anatomic SS		
NRI	0.32	<0.0001
IDI	0.028	0.002
Logistic SS vs. anatomic SS		
NRI	0.26	0.001
IDI	0.046	<0.0001

IDI = integrated discriminatory index; NRI = net reclassification index; other abbreviations as in Table 1.

LM-PCI and did not include patients undergoing CABG. Finally, given the retrospective nature of our analysis, our findings should be considered hypothesis generating.

CONCLUSIONS

The current report, drawn from a large cohort of consecutive patients undergoing LM-PCI, confirms the incremental value of scoring systems combining both clinical and angiographic variables (such as the SS-II) in the decision-making process when facing complex CAD and validates the superiority of the SS-II compared with the purely angiographic SS to risk-stratify patients undergoing LM-PCI.

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APPENDIX For supplemental tables, please see the online version of this article.